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| 10/526,731 | 03/04/2005 | Nicole Francisca Van Poppel | I-2002-017 US | 5787 |

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| EXAMINER | |
|---|---|
| HINES, JANA A | |

| ART UNIT | PAPER NUMBER |
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| 1645 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/526,731 | VAN POPPEL ET AL. | |
| | Examiner | Art Unit | |
| | JaNa Hines | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *21-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 4, 2008 has been entered.

### *Amendment Entry*

2. The amendment filed November 5, 2008 has been entered. Claims 21 and 33 have been amended. Claims 1-20 and 36-38 are cancelled. Claims 21-35 are under consideration in this office action.

### *Withdrawal of Rejections*

3. The following objections and rejections are withdrawn in view of applicants' amendments and arguments:

a) The rejection of claims 21, 28-32 and 34-35 under 35 U.S.C. 102(b) as being anticipated by Wirtz et al., (1999. Molecular and Biochem. Parasit. Vol. 99: 89-101);

b) The rejection of claims 21-27 and 29-31 under 35 U.S.C. 103(a) as being unpatentable over Sutherland et al., (1996. Experimental Parasitol. Vol. 83 :125-133) in view of Xu et al., (WO 98/37185).

***Response to Arguments***

4. Applicant's arguments filed December 4, 2008 have been fully considered but they are not persuasive.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The rejection of claims 21, 28-32 and 34-35 under 35 U.S.C. 103(a) as being unpatentable over Titus et al., (1995. PNAS, Microbio. Vol. 92:10267-10271) in view of Yan et al., (2001. Mol. & Biochem. Parasitol. Vol.112:61-69) is maintained for reasons already of record.

Applicants argue that the result of limiting ribosome synthesis, and therefore the replication of the parasite itself after infecting cells, is not suggested in the prior art, and there would be no suggestion of using procedures that may be found in the prior art to use an inducible promoter to control the expression of the ribosomal protein gene. However the tetracycline repressor/operator system has been used to regulate transcription. In the absence of the inducer, TetR binds and suppresses transcription. Thus, the system of Yan et al., teach a promoter that can be switched on and off, regulating the expression of ribosomal

protein genes by inhibiting transcription, whereby ribosome synthesis is limited, thereby limiting parasite replication in infected cells.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, One of ordinary skill in the art would have a reasonable expectation of success by incorporating the ribosomal protein gene under the control of an inducible promoter because Yan et al., teach that an inducible system advantageously provides stringent regulation of gene expression in *Leishmania,* thereby allowing much lower amounts of tetracycline in order to function effectively. Furthermore, no more than routine skill would have been required to incorporate the ribosomal protein gene under the control of an inducible promoter since Yan et al., teach that conventional gene replacements strategies are unlikely to be useful in the production of stable live attenuated cell lines. Therefore applicants' argument is not persuasive and the rejection is maintained.

***New Grounds of Rejection Necessitated By Amendments***

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 21, 28-32 and 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Wirtz et al., (Science. 1995. Vol. 528(5214), pages 1179-1183).

Claim 21 is drawn to an attenuated live parasite of the phylum Apicomplexa, or the family of Trypanosomatidae capable of infecting cells, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter, by which the promoter can be switched on and off, regulating the expression of the ribosomal protein gene, whereby ribosome synthesis is limited, thereby limiting parasite replication in infected cells. Claim 28 is drawn to the parasite belonging to the genus *Trypansoma* or *Leishmania*. Claim 29 is drawn to the inducible promoter being based upon an operator site and a repressor protein capable of reversibly binding said operator site. Claim 30 is drawn to the inducible promoter being inducible by antibiotics. Claim 31 is drawn to the inducible promoter being inducible by tetracycline. Claim 32 is drawn to the tetR system. Claim 34 is drawn to an immunogenic composition comprising the attenuated live parasite and a pharmaceutically acceptable carrier. Claim 35 is drawn to a method for the production of an immunogenic composition, said

method comprising the mixing of the live attenuated parasite according to Claim 21 and a pharmaceutically acceptable carrier.

Wirtz et al., teach inducible gene expression in trypanosomes mediated by a prokaryotic repressor. Wirtz et al., teach an inducible expression system for *T. brucei* that allows precise control of the expression of genes through a range of four orders of magnitude (page 1179-80, col.1). Wirtz et al., teach TetR repressor has served as the basis for the establishment of heterologous repression based inducible systems in fungal, plant and mammalian cells, yielding 1- to 500 fold regulation of transcription by RNA polymerase II or III. Wirtz et al., teach the TetR mediates very tight transcriptional control of gene expression (page 1180, col.1). Wirtz et al., teach the TetR would block transcription initiation start site of trypanosomes when bound very near the transcription start site of a trypanosomes promoter (page 1180, col.1). Wirtz et al., teach the well characterized promoter of the procyclic acidic repetitive protein gene (page 1180, col. 1). Wirtz et al., tech the inducible expression system is a valuable addition to the repertoire of genetic approaches (page 1182, col. 2). Wirtz et al., teach that the TetR can also be used to control Pol I transcription from trypanosomatid rRNA promoters (page 1182, col. 2).

Therefore Wirtz et al., teach the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 21-29 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sutherland et al., (1996. Experimental Parasitol. Vol. 83:125-133) and Durocher (US 2002/0106720) further in view of Gozar et al., (Int. J. of Parasitol. 1995. Vol. 25 (8): 929-938).

Claim 21 is drawn to an attenuated live parasite of the phylum Apicomplexa, or the family of Trypanosomatidae capable of infecting cells, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter, by which the promoter can be switched on and off, regulating the expression of the ribosomal protein gene, whereby ribosome synthesis is limited, thereby limiting parasite replication in infected cells. Claim 22 is drawn to the parasite belonging to the *Coccidia,* the *Piroplasmida* or the *Haemosporida.* Claim 23 is drawn to the parasite belonging to the family of the *Eimeridiidae, Cryptosporidiidae* or *Sarcocystidae.* Claim 24 is drawn to the parasite belonging to the genus *Eimeria, Cryptosporidium, Toxoplasma, Sarcocystis* or *Neospora.* Claim 25 is drawn to the parasite belonging to the family of the *Babesiidae* or the *Theileriidae.* Claim 26 is drawn the parasite belonging to the genus *Babesia* or *Theileria.* Claim 27 is drawn to the parasite belonging to the genus Plasmodium.

Claim 29 is drawn to the inducible promoter being based upon an operator site and a repressor protein capable of reversibly binding said operator site. Claim 33 is drawn to the ribosomal protein gene being the gene encoding L9, S3, plastid-S9 or S 13, of *Toxoplasma gondii*. Claim 34 is drawn to an immunogenic composition comprising the attenuated live parasite and a pharmaceutically acceptable carrier. Claim 35 is drawn to a method for the production of an immunogenic composition, said method comprising the mixing of the live attenuated parasite according to Claim 21 and a pharmaceutically acceptable carrier.

Sutherland et al., teach the attenuation of *Theileria* cell lines will afford protection from challenges and have been used for the development of live attenuated vaccines (page 125, col. 2). Sutherland et al., teach the selection of other avirulent apicomplexan protozoa which have resulted in reduced virulence (page 126, co1.1). Sutherland et al., teach live attenuated *Babesia* and *Plasmodium* vaccines (page 126, col. 1). Sutherland et al., teach desire and need to control gene expression in such parasites. However Sutherland et al., do not teach a ribosomal protein gene under the control of an inducible promoter.

Durocher teaches an expression system for the expression of the desired gene which comprises an inducible promoter operably linked to a DNA sequence comprising the coding region of the desired gene (col. 2, lines 30-34). Durocher teaches the inducible promoter allows tight regulation of its expression (col. 4, lines 40-43). Durocher teaches the desired gene is or gene of interest whose

expression is associated with a defined physiological or pathological effect with the organisms, (col. 4, lines 56-60). The gene may be a protozoan gene selected from, but not limited to *Trypanosoma, Plasmodium, Leishmania, Toxoplasma, Babesia* and *Cryptosporidiosis* (col. 5, lines 31-37). Durocher teaches the expression system are constructed using standard recombinant DNA techniques wherein the transcriptional promoter is upstream of the DNA sequence which is reverse transcripts of the inducible translation regulator and the RNA stabilizing sequence (col. 6, lines 21-28). However, Durocher does not specifically teach a ribosomal protein gene.

Gozar et al., teach an organelle-like small subunit ribosomal RNA gene from *Babesia bovis*. Gozar et al., teach a 35kbp encoding an RNA polymerase (page 930, col.1). The SSU rRNA gene from a number of species also showed high identity to the gene from *P. falciparum* (page 930, col.1). Gozar et al., teach DNA isolation, amplification, cloning and sequencing (page 930). Gozar et al., teach the rRNA gene is highly conserved across various phyla (page 931, col.2). Gozar et al., teach the putative binding sites for streptomycin and tetracycline and show that SSU rRNA is functional in protein synthesis (page 934).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the attenuated live parasite of Sutherland et al., which incorporates a ribosomal protein gene under the control of an inducible promoter as taught by Durocher and Gozar et al., in order to provide a significant advance in the art. One of ordinary skill in the art would have a reasonable expectation of success by incorporating the ribosomal protein gene under the control of an

inducible promoter because Durocher and Gozar et al., teach that an inducible system advantageously provides stringent regulation of gene expression in prokaryotes. Furthermore, no more than routine skill would have been required to incorporate the ribosomal protein gene under the control of an inducible promoter since the art teaches the desire and need to control gene expression in a wide variety of expression systems by incorporating a ribosomal protein gene under the control of an inducible promoter. Finally it would have been prima facie obvious to combine the invention of Sutherland et al., Durocher and Gozar et al., to advantageously achieve a live attenuated prokaryotic cell line having a high induced level.

***Conclusion***

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645